The effect of fracture recency on observed 10-year fracture probability : A registry-based cohort study

Leslie, William D., Morin, Suzanne N., Lix, Lisa M., McCloskey, Eugene V., Johansson, Helena, Harvey, Nicholas C. and Kanis, John A.

Leslie William Donald (Orcid ID: 0000-0002-1056-1691)
Morin Suzanne Nicole (Orcid ID: 0000-0002-4317-492X)
Lix Lisa (Orcid ID: 0000-0001-8685-3212)
McCloskey Eugene (Orcid ID: 0000-0003-0177-8140)
Harvey Nicholas C (Orcid ID: 0000-0002-8194-2512)

The Effect of Fracture Recency on Observed 10-year Fracture Probability: A Registry-Based Cohort Study

Short Title: Effect of Fracture Recency on Observed Fracture Probability

William D Leslie MD MSc ORCID 0000-0002-1056-1691 [1]: bleslie@sbgh.mb.ca
Suzanne N Morin MD MSc[2]: suzanne.morin@mcgill.ca
Lisa M Lix PhD [1]: lisa.lix@umanitoba.ca
Eugene V. McCloskey MD [3]; e.v.mccloskey@sheffield.ac.uk
Helena Johansson PhD [3,4]; helena@statiq.se
Nicholas C. Harvey MD PhD [5,6]; nch@mrc.soton.ac.uk
John A. Kanis MD ORCID: 0000-0002-3129-4326 [3,4]; jakanis@outlook.com

Affiliations:

(1) University of Manitoba, Winnipeg, Canada;
(2) McGill University, Montreal, Canada;
(3) Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK;
(4) Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne;
(5) MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK;
(6) NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.

Author for Correspondence and Reprints:
Dr. William D. Leslie
Department of Medicine (C5121). 409 Tache Avenue
Winnipeg, Manitoba, Canada R2H 2A6
Phone: 204-237-2311 Fax: 204-237-2007 Email: bleslie@sbgh.mb.ca

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ABSTRACT

FRAX® estimates 10-year fracture major osteoporotic fracture (MOF) and hip fracture probability from multiple risk factors. FRAX does not consider prior fracture site or time since fracture. Fracture risk is greater in the initial 2-year post-fracture period (imminent risk), implying that FRAX may underestimate risk in this setting. We used the population-based Manitoba Bone Mineral Density (BMD) Program registry to examine the effect of fracture recency and site on incident fracture risk predictions using FRAX. We identified women age 40 years or older with baseline BMD and FRAX scores. Observed fracture outcomes to 10 years were compared with predicted 10-year fracture probability stratified by prior fracture status: none, recent (<2 years [median 0.3 years]), remote (≥2 years [median 10.6 years]). For women with recent fractures, we also examined proposed multipliers to adjust FRAX for the effect of fracture recency and site. The cohort comprised 33,465 women age 40-64 years (1,897 recent fracture, 2,120 remote fracture) and 33,806 women age ≥65 years (2,365 fracture, 4,135 remote fracture). Observed fracture probability was consistent with predicted probability in most analyses. In women age 40-64 years, there was a significant effect of recent vertebral and humerus fracture on MOF (observed to predicted 1.61 and 1.48, respectively) but these effects were still lower than the proposed multipliers (2.32 and 1.67, respectively). No significant effect of fracture recency was seen following hip or forearm fracture in either age group. Our findings contribute to accumulating evidence of the importance of recent fracture. The effect of fracture recency was not consistent across fracture sites, and with a lower magnitude than previously reported. Further quantification of effect size and specificity in additional independent cohorts is warranted to validate and refine recent-fracture multipliers in fracture risk assessment.

KEY WORDS: Osteoporosis; Fracture; Imminent risk; Major osteoporotic fracture; Population-based cohort study; FRAX

INTRODUCTION

Osteoporosis is characterized by bone fragility and susceptibility to fracture, with large health consequences and costs for the individual and society (1). Prior fragility fracture is a well-established risk factor for a future fracture (2-4) and this excess risk extends for up to at least 25 years (5). The relative risk of having a subsequent fracture is approximately 2-fold higher for most types of prior fracture. Several studies demonstrate that the increase in risk is not constant with time, is greatest immediately after an index fracture, wanes progressively over time, but always remains higher than that of the general population (5-12). An early transient phase of particularly high risk has been termed "imminent risk" (12).

The FRAX® tool estimates 10-year fracture probability for major osteoporotic fracture (MOF; hip, clinical vertebral, humerus, forearm) and hip fracture alone based upon a small number of clinical risk factors that includes previous fracture history. FRAX does not consider, however, the site of fracture or the recency of fracture in this calculation. For this reason, FRAX "multipliers" have been developed from a population-based cohort from Iceland (12) to adjust for the effect of a recent fracture (preceding 2 years), overall and stratified by MOF site, to capture this imminent risk (13). These multipliers are age-dependent, decreasing with age in both men and women. For example, assume that a woman age 60 years with a prior fracture and body mass index 25 kg/m^2 had a 10-year probability of a MOF of 13% (Canadian FRAX tool). If the woman had actually sustained a clinical vertebral fracture within the past 2 years, then the estimate would be uplifted by a factor of 1.84 to 23.9% (13 × 1.84).

These recent-fracture multipliers have not been directly validated in populations with complete information on all FRAX risk factors, including bone mineral density (BMD). The current analysis was performed to characterize the effect of previous fracture, stratified as recent

(<2 years) versus remote (≥2 years) on fracture risk, performance of FRAX, and the utility of recent-fracture multipliers. Analyses were stratified by age (less than 65 years versus 65 years or older) to explore the age-dependency noted above. Previous analyses of time-dependency in fracture risk have used date of first fracture as the index date. However, this does not reflect the clinical perspective where BMD testing and fracture risk assessment typically occur many months or years later. Therefore, the current complementary analysis examines the importance of time since prior fracture on future fracture risk where the index date is the date of BMD testing.

METHODS

Study Population

In the Canadian Province of Manitoba (population 1.3 million in 2017), health services are provided to virtually all residents through a public healthcare system. Dual-energy x-ray absorptiometry (DXA)-based BMD testing has been managed as an integrated clinical program since 1997; criteria for testing have been published and include screening at age 65 years for women and in men and younger women with additional risk factors (14). The program maintains a database of all DXA results which can be linked with other provincial population-based computerized health databases through an anonymous personal identifier. The DXA database has completeness and accuracy in excess of 99% (15).

The study population consisted of all women age 40 years or older with baseline DXA scans from January 1, 1996 to March 31, 2016, at least 5 years of coverage before and at least 2 years (maximum 10 years) of observation after the baseline assessment (index date). Women lost to follow-up due to migration prior to 2 years (<2%) were excluded (death was not reason for exclusion since it was treated as a competing endpoint). We excluded those not registered for health care in Manitoba and without coverage after the baseline BMD. For those with more than

one qualifying examination, only the first was included. The study was approved by the Health Research Ethics Board for the University of Manitoba.

Fracture ascertainment

Manitoba Health records for the study population since 1984 were assessed for the presence of fracture diagnostic codes prior to BMD assessment. Time since fracture to the index date (BMD testing) was stratified as <2 years versus ≥2 years. Fractures were assessed through a combination of hospital discharge abstracts (diagnoses and procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] prior to 2004 and International Classification of Diseases, Tenth Revision, Canadian Enhancements [ICD-10-CA] thereafter) and physician billing claims (coded using ICD-9-CM) using previously validated algorithms (16, 17). Analyses were based upon hip, clinical vertebral, forearm, and humerus fracture diagnostic codes (collectively designated "major osteoporotic fractures", MOF). Similar definitions were used to identify incident fractures occurring after BMD assessment up to March 31, 2018. Prior fractures and incident fractures with high-trauma codes (representing ~5% of MOF (18)) were excluded. To minimize potential misclassification of prior incident fractures, same-site refracture was allowed after 3 months for hip and after 6 months for non-hip fractures, an interval similar to or shorter than has been used for similar analyses.(5, 10, 11, 19-21) To enhance the diagnostic specificity for same-site vertebral and humerus fractures, we required more than one site-specific x-ray code which we have previously shown has high sensitivity and temporal specificity for an acute fracture (22).

Bone Mineral Density and FRAX Calculation

Hip DXA scans were performed and analyzed in accordance with manufacturer recommendations. Hip T-scores (number of SDs above or below young adult mean BMD) were calculated from NHANES III white female reference values (23). The program's quality assurance is under strict supervision by a medical physicist (14). The cross-calibrated instruments used for this study (1 DPX, 3 Prodigy and 3 iDXA, GE/Lunar Healthcare, Madison WI) exhibited equivalent phantom calibration and stable long-term performance (coefficient of variation <0.5%). BMD T-scores from the instruments were all based upon the same reference databases. All reporting physicians and supervising technologists are required to maintain DXA certification with the International Society for Clinical Densitometry (ISCD).

Ten-year probability of a major osteoporotic fracture risk was calculated using the fracture risk assessment tool, Canadian version (FRAX® Desktop Multi-Patient Entry, version 3.7) (24, 25). Briefly, age, body mass index (BMI), femoral neck BMD and other data required for calculating fracture probability with FRAX were assessed from measurements (height and weight) and information collected directly from subjects through the intake questionnaire which was reviewed at the time of DXA scanning (26). Questionnaire information was supplemented with population-based healthcare data (hospital discharge abstracts, medical claims diagnoses, province-wide retail pharmacy database) as previously described, thereby ensuring complete information in virtually all subjects (27-29). Prior fracture was included as the traditional FRAX input variable, without considering site or time since fracture. The Canadian FRAX tool was calibrated using nationwide hip fracture and mortality data as previously described (25). Predictions agree closely with observed fracture risk in our population (30, 31).

For each individual with recent fractures (within 2 years), we calculated an age- and site-specific recent-fracture multiplier (with age as a continuous measure). The proposed Icelandic

site-specific multipliers reported values for fixed ages (40, 50, 60, 70, 80 years) (13). These previously published values were interpolated using a polynomial function as a function of age (all fitted $r^2 > 0.98$).

Statistical Analysis

Statistical analyses were performed with Statistica (Version 13.0, StatSoft Inc, Tulsa, OK). Descriptive statistics for demographic and baseline characteristics are presented as mean ± standard deviation (SD) for continuous variables and frequency (%) for categorical variables. Multivariable logistic regression models were constructed to examine the effect of prior MOF, stratified by time and site, on an incident fracture in the next 2 years (referent no prior fracture). All models were adjusted for age (years as a continuous measure), BMI, parental hip fracture, smoking status, glucocorticoid use, rheumatoid arthritis diagnosis, secondary osteoporosis diagnosis, high alcohol intake, and T-score at the femoral neck as previously described (27-29). Cox proportional hazards regression was not performed to examine fracture risk over 10 years due to violation of the proportional hazards assumption. Therefore, 10-year fracture probability, estimated by FRAX and 10-year cumulative fracture probability observed in the population using a non-parametric method (32, 33), were directly compared as a measure of FRAX calibration, stratified by age and prior fracture status. Mortality was treated as a competing endpoint in constructing the cumulative probability curves and gives results equivalent to the Klein-Anderson method (33, 34). Cumulative fracture probability curves were compared using the log-rank test. Calibration ratios (observed divided by predicted 10-year fracture probability) with 95% confidence intervals (CI) were estimated for each age and prior fracture subgroup. A ratio of unity indicates excellent concordance between the observed and predicted measures (risk

is accurately estimated); a value greater than one indicates that observed fracture risk exceeds predicted (risk is underestimated) whereas a value less than one indicates that observed fracture risk is below predicted (risk is overestimated). If a fracture in the prior 2 years increases refracture risk similar to what was seen in the Iceland cohort then we would expect to see miscalibration in the recent fracture subgroup, with ratios substantially greater than one and of a magnitude similar to the proposed recent-fracture multipliers. For those with a recent MOF we also individually estimated 10-year fracture probability after applying the previously published recent-fracture multiplier (age- and site-specific), (13) to determine whether this improved the agreement between observed and predicted risk.

RESULTS

Study population

Table 1 provides baseline characteristics stratified by age less than 65 years (N = 33,465, mean age 55.3 years) versus age 65 years or older (N = 33,806, mean age 73.4 years). As expected, baseline BMD was higher with lower prior fracture prevalences and calculated FRAX probabilities in younger versus older women. For example, the prevalence of MOF in the preceding 2 years was significantly lower in younger versus older women (5.7% versus 7.0%) and was also lower for MOF that had occurred more than 2 years earlier (6.3% versus 12.2%). For those with a recent fracture, median time since fracture was 0.3 years (interquartile range 0.2-0.7 years) and for those with remote prior fracture was 10.6 years (interquartile range 4.7-16.1 years). Similar results were seen when stratified by prior fracture site (data not shown).

Fractures in the initial 2 years of observation

In the initial 2 years of observation up there were 1,206 incident MOF (364 and 842 for women aged 40-64 years and ≥ 65 years, respectively) and 263 incident hip fractures (32 and 231 for women aged 40-64 years and ≥ 65 years, respectively). **Table 2** shows that a previous fracture was associated with increased risk for recurrent fracture. For women age less than 65 years, MOF in the prior 2 years was associated with an adjusted OR for repeat MOF of 2.86 (95% CI 2.13 - 3.84) which was significantly greater (p=0.012 for recent vs remote [referent] prior fracture) than if the fracture occurred more than 2 years previously (OR 1.68, 95% CI 1.19 - 2.37). For women age 65 years or older, the OR for recent prior MOF was 1.99 (95% CI 1.62 - 2.45) which was not significantly greater (p=0.30) than for a fracture that occurred more than 2 years previously (OR 1.76, 95% CI 1.48 - 2.10). Prior MOF was also associated with increased risk for hip fracture in women age less than 65 years, which was numerically but not significantly greater (p=0.63) if the fracture occurred in the previous 2 years (OR 2.89, 95% CI 1.13 – 7.44) versus more than 2 years previously (OR 2.15, 95% CI 0.79 – 5.87). For hip fracture risk in women over age 65 years, the OR for a recent MOF (2.45, 95% CI 1.75 – 3.45) was significantly greater (p=0.009) than if the fracture occurred more than 2 years previously (OR 1.43, 95% CI 1.02 – 2.01). There was a similar non-significant trend in women age less than 65 years (p=0.68).

When the analyses of MOF risk in the first 2 years were stratified by both fracture site and the time since fracture, the only statistically significant effect of recency in women less than 65 years was for a vertebral fracture (p<0.001), with OR 5.94 (95% CI 3.72 – 9.49) when this occurred in the previous 2 years versus 1.24 (95% CI 0.64 – 2.44) when this occurred more than 2 years earlier. There was a non-significant trend for greater risk from a recent humerus fracture (p=0.18) and recent forearm fracture (p=0.68) among women age less than 65 years. For women

age 65 years or older, the only significant time dependency was for a prior hip fracture (p=0.033), with OR 1.91 (95% CI 1.32 – 2.76) when this occurred in the prior 2 years versus 1.04 (95% CI 0.66 – 1.61) when this occurred more than 2 years previously. This time dependency was also seen for a second hip fracture among older women (p=0.002) and for a hip fracture following a humerus fracture (p=0.043). The number of incident hip fractures in women age less than 65 years was insufficient for stratification by prior fracture site.

Fractures in all 10 years of observation

In the 10 years of observation there were 5,057 incident MOF (1,633 and 3,424 for women aged 40-64 years and ≥ 65 years, respectively) and 1,576 incident hip fractures (217 and 1,359 for women aged 40-64 years and ≥ 65 years, respectively). Baseline characteristics were related to fracture outcome as shown in **Supplementary Table 2**. **Figure 1** shows the 10-year cumulative incidence for MOF and hip fracture stratified by age and time since last MOF (all log-rank P <0.001). For women less than age 65 years, recent MOF was associated with an increased risk for subsequent MOF that exceeded the risk for women with no prior fracture or a fracture that occurred more than 2 years previously, and the risk was sustained up to 10 years. In contrast, among women age 65 years or older, there was a slightly greater risk for fracture in the previous 2 years versus fracture more than 2 years previously, but this difference was no longer evident at 10 years, though both groups remained at much higher risk than women with no prior fracture. Similar trends were noted for hip fracture following MOF.

FRAX calibration and recent-fracture multipliers

When the observed 10-year fracture probability was compared with FRAX predicted probability, most calibration ratios tended to be close to unity indicating good calibration (**Table 3**). An effect of fracture within the previous 2 years was seen following a vertebral fracture in women less than age 65 years (calibration ratio 1.61, 95% CI 1.18 – 2.04) and also after a humerus fracture (calibration ratio 1.48, 95% CI 1.05 - 1.92) indicating that FRAX underestimated the true fracture probability. In contrast, for women age 65 years or older, there were no situations where FRAX significantly underestimated MOF probability. The recent-fracture multipliers overestimated the calibration ratios among those with fracture in the previous 2 years except for women age less than 65 years with a humerus fracture. For incident hip fracture (**Table 4**), the recent-fracture multiplier significantly overestimated the observed calibration ratios following recent hip fracture and forearm fracture in women less than age 65 years. Those situations were identified where observed hip fracture probability exceeded predicted probability in women with previous fracture.

Supplemental Table 1 shows the overall effect of recent-fracture multipliers for those with a fracture in the last 2 years, stratified by age and time since fracture. Multipliers were greater in women less than age 65 years versus age 65 years or older (except for the hip fracture multiplier following humerus fracture). The greatest multiplier was seen for MOF after a recent vertebral fracture (mean 2.32) and for hip fracture after a recent hip fracture (mean 3.7) in women age less than 65 years. **Supplemental Figures 1-4** show analyses by previous fracture site.

DISCUSSION

This large clinical registry of individuals undergoing retrospective baseline fracture risk assessment with FRAX and BMD identified evidence of time-dependency in fracture risk. This effect was seen for incident MOF in women age 40 - 64 years after a recent MOF, with a particularly strong effect for recent vertebral fracture as has been reported by others (6, 7, 35). Time-dependency was seen for incident hip fracture in the next 2 years in women age 65 years or older after a recent MOF, with stronger effects for recent hip fracture or humerus fracture. However, these differences were attenuated for fracture risk over 10 years, though FRAX (including prior fracture at any time or site) continued to underestimate fracture risk in women less than age 65 years after recent vertebral fracture (calibration ratio 1.61) or recent humerus fracture (calibration ratio 1.48). Inclusion of previously published multipliers to account for recent fracture tended to overestimate the adjustment required (2.32 versus 1.67, respectively).

To the best of our knowledge, no other studies have been published that directly examined the effect of fracture recency on the performance of FRAX. The Icelandic database used for derivation of the recent-fracture multipliers did not have complete FRAX covariates (only age, sex and date and site of incident fractures), therefore covariates were simulated based upon expected frequency; moreover, this data set did not report BMD measurements (13). Although we confirmed the effect of recent fracture as an indicator of higher fracture risk, in general the effect size was less than predicted from these multipliers. Whether this reflects differences in fracture epidemiology within the populations or methodologic differences is uncertain. A significant difference between the two approaches arose with regards to handling of early same-site fractures. In the Icelandic data set, there was no time restriction, and a large proportion of second fractures occurred at the same site. Identification of same-site fractures in

administrative data is more challenging and requires a fracture-free interval. We used 3 months for hip fracture and 6 months for non-hip fracture, with the additional requirements for orthopedic codes and/or site-specific x-rays to enhance diagnostic specificity as previously reported (22). This interval is similar to or shorter than has been used for similar analyses (5, 10, 11, 19-21), but could still lead to undercounting of fractures within the initial 3-6 months, though these fractures may not be preventable with early treatment. Banefelt et al.(19) reported that the rate of subsequent fractures was much higher in the first month and remained steady between 4 and 24 months, suggesting that more work is needed to elucidate this time course. It will be important to examine other large data sets using a variety of methods for fracture ascertainment to assess the robustness of the recent-fracture multipliers and their applicability in routine clinical practice.

Current findings from the Manitoba BMD Registry are consistent with a population-based analysis of time-dependency in early MOF and hip re-fractures for all women and men in the Province of Manitoba (2,105 women, mean age 74.1±10.6 years and 7,589 men, mean age 71.8±11.2 years with a first MOF after age 50 years) (36). Among fracture cases there was a tendency for rates to decline gradually in all subgroups except younger women, but these temporal trends appeared monotonic without an obvious change in earlier versus later years. Findings were robust to shortening the same-site re-fracture interval, examining fractures at different sites, analyses limited to those surviving at least five years, and examining monthly fracture rates during the initial year. Whereas some studies have reported varying degrees of imminent risk, the magnitude of effect is very heterogeneous (5-12). Several studies have shown no convincing evidence of time-dependency is re-fracture risk in that the relative risk at 2 years

was no greater than the relative risk at 5 years (20, 21, 37-39). The source of this heterogeneity is uncertain.

Limitations to our analyses are acknowledged. As stated earlier, early same-site fractures (within 3-6 months) could have been excluded. However, identification, investigation, and initiation of treatment with onset of antifracture effect would almost certainly exceed 3-6 months, and early same-site refractures occurring within this time window are unlikely to be preventable. Detection of vertebral fractures is particularly challenging and only clinical vertebral fractures can be ascertained. The fracture definitions that were used have been directly validated based upon x-ray review and enhanced by the use of site-specific x-ray codes (22). We did not exclude the small number of individuals on treatment post fracture (14.0%), though the known large post fracture care gap would mitigate this effect. Moreover, our approach is similar to the Icelandic comparator, which did not exclude individuals receiving treatment. Additionally, lifestyle factors cannot be assessed from administrative data. Falls is not currently an input variable to FRAX, but may be one of the mediating factors contributing to early refracture risk since falls often occur in succession and increase fracture risk independently from FRAX (40). The decrease in muscle strength and physical performance seen during the first months after fracture may also be important (41). Finally, the Manitoba BMD Registry population is almost exclusively (>97%) of White ethnicity, and we cannot be certain that our findings will apply to other populations or to men.

In summary, the risk of MOF and hip re-fracture was elevated over 10 years. Our findings present further evidence for the excess fracture risk associated with recent fracture, but the effect of fracture recency was not consistent across fracture sites, and with a lower magnitude than in recent estimates from the Reykjavik cohort. Further quantification of effect size and

specificity in additional independent cohorts is warranted to validate and refine recent-fracture multipliers in fracture risk assessment. Meanwhile, a first fracture should continue to be regarded as a major risk factor for a second fracture and calls for a thorough clinical evaluation and appropriate initiation of non-pharmacologic interventions, medications and falls prevention to reduce that risk.

DETAILS OF CONTRIBUTORS

All authors substantially contributed to: conception (WDL) and design (WDL, LML), or analysis (WDL, SNM, LML) and interpretation of data (WDL, SNM, LML, EVN, HJ, NCH, JAK); drafting the article (WDL) or revising it critically for important intellectual content (WDL, SNM, LML, EVN, HJ, NCH, JAK); and final approval of the version to be published (WDL, SNM, LML, EVN, HJ, NCH, JAK). WDL accepts full responsibility for the work and/or the conduct of the study, had full access to all the data, and controlled the decision to publish.

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CONFLICTS OF INTEREST

Eugene McCloskey: Nothing to declare for the context of this paper, but has received ad hoc consultancies / speaking honoraria and/or research funding from Amgen, Bayer, General Electric, GSK, Fresenius Kabi, Hologic, Lilly, Merck Research Labs, Novartis, Novo Nordisk, Nycomed, Ono, Pfizer, ProStrakan, Roche, Sanofi-Aventis, Servier, Tethys, UCB and Warner-Chilcott.

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John Kanis: JAK is the architect of FRAX® but has no financial interest.

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DATA AVAILABILITY

Data sharing is not permitted under the Researcher Agreement with Manitoba Health and Seniors Care. However, researchers may apply for data access through the Health Research Ethics Board of the University of Manitoba and the Health Information and Privacy Committee of Manitoba Health.

REFERENCES

1. Compston JE, McClung MR, Leslie WD. Osteoporosis. The Lancet. 2019;393(10169):364-76.
2. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, III, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. 2000;15(4):721-39.
3. Haentjens P, Johnell O, Kanis JA, Bouillon R, Cooper C, Lamraski G, et al. Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men. J Bone Miner Res. 2004;19(12):1933-44.
4. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004;35(2):375-82.
5. Morin SN, Yan L, Lix LM, Leslie WD. Long-term risk of subsequent major osteoporotic fracture and hip fracture in men and women: a population-based observational study with a 25-year follow-up. Osteoporos Int. 2021;32(12):2525-32.
6. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. 2001;285(3):320-3.
7. Johnell O, Oden A, Caulin F, Kanis JA. Acute and long-term increase in fracture risk after hospitalization for vertebral fracture. Osteoporos Int. 2001;12(3):207-14.
8. Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P. Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001. J Bone Miner Res. 2009;24(7):1299-307.
9. van Geel TA, van Helden S, Geusens PP, Winkens B, Dinant GJ. Clinical subsequent fractures cluster in time after first fractures. Ann Rheum Dis. 2009;68(1):99-102.
10. Giangregorio LM, Leslie WD, Manitoba Bone Density P. Time since prior fracture is a risk modifier for 10-year osteoporotic fractures. J Bone Miner Res. 2010;25(6):1400-5.
11. Balasubramanian A, Zhang J, Chen L, Wenkert D, Daigle SG, Grauer A, et al. Risk of subsequent fracture after prior fracture among older women. Osteoporos Int. 2019;30(1):79-92.
12. Johansson H, Siggeirsdottir K, Harvey NC, Oden A, Gudnason V, McCloskey E, et al. Imminent risk of fracture after fracture. Osteoporos Int. 2017;28(3):775-80.
13. Kanis JA, Johansson H, Harvey NC, Gudnason V, Sigurdsson G, Siggeirsdottir K, et al. Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. Osteoporos Int. 2020;31(10):1817-28.
14. Leslie WD, Metge C. Establishing a regional bone density program: lessons from the Manitoba experience. J Clin Densitom. 2003;6(3):275-82.
15. Leslie WD, Caetano PA, Macwilliam LR, Finlayson GS. Construction and validation of a population-based bone densitometry database. J Clin Densitom. 2005;8(1):25-30.
16. Lix LM, Azimaee M, Osman BA, Caetano P, Morin S, Metge C, et al. Osteoporosis-related fracture case definitions for population-based administrative data. BMC Public Health. 2012;12:301.
17. Epp R, Alhrbi M, Ward L, Leslie WD. Radiological validation of fracture definitions from administrative data. J Bone Miner Res. 2018;33(Supp 1):S275.

18. Leslie WD, Schousboe JT, Morin SN, Martineau P, Lix LM, Johansson H, et al. Fracture risk following high-trauma versus low-trauma fracture: a registry-based cohort study. Osteoporos Int. 2020;31(6):1059-67.
19. Banefelt J, Akesson KE, Spangeus A, Ljunggren O, Karlsson L, Strom O, et al. Risk of imminent fracture following a previous fracture in a Swedish database study. Osteoporos Int. 2019;30(3):601-9.
20. Soreskog E, Strom O, Spangeus A, Akesson KE, Borgstrom F, Banefelt J, et al. Risk of major osteoporotic fracture after first, second and third fracture in Swedish women aged 50years and older. Bone. 2020;134:115286.
21. Jung HS, Jang S, Chung HY, Park SY, Kim HY, Ha YC, et al. Incidence of subsequent osteoporotic fractures after distal radius fractures and mortality of the subsequent distal radius fractures: a retrospective analysis of claims data of the Korea National Health Insurance Service. Osteoporos Int. 2021;32(2):293-9.
22. Leslie WD, Epp R, Morin SN, Lix LM. Assessment of site-specific X-ray procedure codes for fracture ascertainment: a registry-based cohort study. Arch Osteoporos. 2021;16(1):107.
23. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int. 1998;8(5):468-89.
24. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. Bone. 2009;44(5):734-43.
25. Leslie WD, Lix LM, Langsetmo L, Berger C, Goltzman D, Hanley DA, et al. Construction of a FRAX(R) model for the assessment of fracture probability in Canada and implications for treatment. Osteoporos Int. 2011;22(3):817-27.
26. Bisson EJ, Finlayson ML, Ekuma O, Marrie RA, Leslie WD. Accuracy of FRAX(R) in people with multiple sclerosis. J Bone Miner Res. 2019.
27. Leslie WD, Morin SN, Lix LM, Niraula S, McCloskey EV, Johansson H, et al. Performance of FRAX in Women with Breast Cancer Initiating Aromatase Inhibitor Therapy: A Registry-Based Cohort Study. J Bone Miner Res. 2019;34(8):1428-35.
28. Peschken CA, Hitchon CA, Garland A, Bernstein CN, Chen H, Fransoo R, et al. A Population-based Study of Intensive Care Unit Admissions in Rheumatoid Arthritis. J Rheumatol. 2016;43(1):26-33.
29. Yang S, Leslie WD, Yan L, Walld R, Roos LL, Morin SN, et al. Objectively Verified Parental Hip Fracture Is an Independent Risk Factor for Fracture: a Linkage Analysis of 478,792 Parents and 261,705 Offspring. J Bone Miner Res. 2016;31(9):1753-9.
30. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA, et al. Independent clinical validation of a Canadian FRAX tool: fracture prediction and model calibration. J Bone Miner Res. 2010;25(11):2350-8.
31. Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, et al. Fracture prediction and calibration of a Canadian FRAX(R) tool: a population-based report from CaMos. Osteoporos Int. 2011;22(3):829-37.
32. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer. 2004;91(7):1229-35.
33. Leslie WD, Lix LM, Wu X, Manitoba Bone Density P. Competing mortality and fracture risk assessment. Osteoporos Int. 2013;24(2):681-8.

34. Klein JP, Gerster M, Andersen PK, Tarima S, Perme MP. SAS and R functions to compute pseudo-values for censored data regression. Comput Methods Programs Biomed. 2008;89(3):289-300.
35. Toth E, Banefelt J, Akesson K, Spangeus A, Ortsater G, Libanati C. History of Previous Fracture and Imminent Fracture Risk in Swedish Women Aged 55-90 Years Presenting with a Fragility Fracture. J Bone Miner Res. 2020.
36. Leslie WD, Yan L, Lix LM, Morin SN. Time dependency in early major osteoporotic and hip re-fractures in women and men aged 50 years and older: a population-based observational study. Osteoporos Int. 2022;33(1):39-46.
37. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA. 2007;297(4):387-94.
38. Chapurlat RD, Bauer DC, Nevitt M, Stone K, Cummings SR. Incidence and risk factors for a second hip fracture in elderly women. The Study of Osteoporotic Fractures. Osteoporos Int. 2003;14(2):130-6.
39. van Staa TP, Leufkens HG, Cooper C. Does a fracture at one site predict later fractures at other sites? A British cohort study. Osteoporos Int. 2002;13(8):624-9.
40. Leslie WD, Morin SN, Lix LM, Martineau P, Bryanton M, McCloskey EV, et al. Fracture prediction from self-reported falls in routine clinical practice: a registry-based cohort study. Osteoporos Int. 2019;30(11):2195-203.
41. Szulc P. Impact of Bone Fracture on Muscle Strength and Physical Performance-Narrative Review. Curr Osteoporos Rep. 2020;18(6):633-45.

Figure captions

Figure 1 Observed cumulative incidence for fracture major osteoporotic fracture (MOF) probability (left panels) and hip fracture probability (right panels) stratified by age and time since last MOF (N=33,465 women age 40-64 years, N=33,806 age $\geq$ 65 years).

Figure 2 Predicted (blue bar) versus observed (red bar) 10-year fracture major osteoporotic fracture (MOF) probability and hip fracture probability stratified by time since last MOF (N=33,465 women age 40-64 years, N=33,806 age $\geq$ 65 years). For those with fracture in the last 2 years, predicted risk was further adjusted using the recent-fracture multipliers (green bar). Error bars are 95% confidence intervals for observed risk.

Table 1 Baseline characteristics of included women from the Manitoba BMD Registry.

Characteristic	Age 40-64 years N=33,465	Age ≥ 65 years N=33,806
Age	55.3 ± 5.9	73.4 ± 6.5
T-score femoral neck	-1.1 ± 0.9	-1.7 ± 0.9
FRAX MOF with BMD (%)	6.4 ± 4.2	14.1 ± 7.8
FRAX HIP with BMD (%)	0.7 ± 1.4	4.0 ± 4.8
Any prior MOF, <2 years	1897 (5.7)	2365 (7.0)
Any prior MOF, >2 years	2120 (6.3)	4135 (12.2)
Prior vertebral fracture, <2 years	305 (0.9)	482 (1.4)
Prior vertebral fracture, >2 years	570 (1.7)	775 (2.3)
Prior hip fracture, <2 years	138 (0.4)	422 (1.2)
Prior hip fracture, >2 years	63 (0.2)	394 (1.2)
Prior humerus fracture, <2 years	350 (1.0)	486 (1.4)
Prior humerus fracture, >2 years	383 (1.1)	869 (2.6)
Prior forearm fracture, <2 years	1143 (3.4)	1052 (3.1)
Prior forearm fracture, >2 years	1375 (4.1)	2850 (8.4)

Data are mean ± SD; N (%). MOF, major osteoporotic fracture; BMD, bone mineral density.

Leslie William Donald (Orcid ID: 0000-0002-1056-1691)
Morin Suzanne Nicole (Orcid ID: 0000-0002-4317-492X)
Lix Lisa (Orcid ID: 0000-0001-8685-3212)
McCloskey Eugene (Orcid ID: 0000-0003-0177-8140)
Harvey Nicholas C (Orcid ID: 0000-0002-8194-2512)

Table 2 Adjusted odds ratios (95% confidence intervals, OR [CI]) for incident fracture in the first 2 years after BMD assessment according to age and prior fracture recency (N=33,465 women age 40-64 years, N=33,806 age ≥ 65 years).

	Time since fracture	Age 40-64 years OR (95%CI), Incident MOF	Age ≥65 years OR (95%CI), Incident MOF
Any prior MOF	<2 years	**2.86 (2.13-3.84)***	**1.99 (1.62-2.45)**
	≥2 years	**1.68 (1.19-2.37)**	**1.76 (1.48-2.10)**
Prior vertebral fracture	<2 years	**5.94 (3.72-9.49)*****	**2.69 (1.91-3.78)**
	≥2 years	1.24 (0.63-2.44)	**2.23 (1.65-3.01)**
Prior hip fracture	<2 years	0.64 (0.15-2.69)	**1.91 (1.32-2.76)***
	≥2 years	0.82 (0.11-6.00)	1.04 (0.66-1.61)
Prior humerus fracture	<2 years	**3.82 (2.27-6.43)**	**2.05 (1.38-3.05)**
	≥2 years	**2.24 (1.23-4.09)**	**1.67 (1.24-2.26)**
Prior forearm fracture	<2 years	**1.58 (1.01-2.49)**	0.97 (0.66-1.43)
	≥2 years	1.40 (0.92-2.12)	**1.46 (1.20-1.78)**
	Time since fracture	OR (95%CI), Incident Hip	OR (95%CI), Incident Hip
Any prior MOF	<2 years	**2.89 (1.13-7.44)**	**2.45 (1.75-3.45)****
	≥2 years	2.15 (0.79-5.87)	**1.43 (1.02-2.01)**
Prior vertebral fracture	<2 years	Insufficient numbers	1.03 (0.45-2.37)
	≥2 years	Insufficient numbers	1.42 (0.78-2.60)
Prior hip fracture	<2 years	Insufficient numbers	**2.99 (1.85-4.83)****
	≥2 years	Insufficient numbers	0.80 (0.38-1.69)
Prior humerus fracture	<2 years	Insufficient numbers	**3.65 (2.09-6.36)***
	≥2 years	Insufficient numbers	**1.72 (1.02-2.89)**
Prior forearm fracture	<2 years	Insufficient numbers	1.47 (0.82-2.65)
	≥2 years	Insufficient numbers	1.36 (0.95-1.97)

Referent: no prior fracture. Adjusted for age, body mass index, parental hip fracture, smoking status, glucocorticoid use, rheumatoid arthritis diagnosis, secondary osteoporosis diagnosis, high alcohol intake, and T-score at the femoral neck. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ for recent vs remote [referent] prior fracture. Boldface font indicates a p-value $< \alpha = 0.05$.

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Table 3 Calibration ratios for incident major osteoporotic fracture (observed vs predicted 10-year fracture probability with 95% confidence interval) and mean recent-fracture multiplier, analyzed according to age and prior fracture recency (N=33,465 women age 40-64 years, N=33,806 age ≥ 65 years).

Age 40-64 years	No prior fracture	≥ 2 years	< 2 years	Mean multiplier
Any Prior MOF	0.97 (0.92-1.02)	0.79 (0.67-0.91)	1.04 (0.89-1.19)	1.56***
Prior Vertebral	0.88 (0.84-0.92)	0.84 (0.59-1.09)	**1.61 (1.18-2.04)**	2.32**
Prior Hip	0.89 (0.85-0.93)	0.55 (0.09-1.02)	0.92 (0.48-1.37)	1.82***
Prior Humerus	0.88 (0.84-0.92)	1.03 (0.72-1.34)	**1.48 (1.05-1.92)**	1.67
Prior Forearm	0.89 (0.84-0.93)	0.97 (0.81-1.13)	0.90 (0.72-1.09)	1.29***
Age ≥ 65 years	No prior fracture	≥ 2 years	< 2 years	Mean Multiplier
Any Prior MOF	0.99 (0.95-1.02)	0.86 (0.8-0.92)	0.91 (0.83-1.00)	1.16***
Prior Vertebral	0.89 (0.86-0.92)	1.07 (0.92-1.22)	1.12 (0.94-1.31)	1.34*
Prior Hip	0.91 (0.88-0.94)	0.71 (0.56-0.85)	0.87 (0.69-1.05)	1.04
Prior Humerus	0.90 (0.87-0.93)	0.91 (0.77-1.04)	0.93 (0.74-1.13)	1.31***
Prior Forearm	0.91 (0.88-0.94)	0.90 (0.83-0.98)	0.72 (0.59-0.84)	1.06***

* p<0.05, ** p<0.01, *** p<0.001 for recent-fracture multiplier in those with recent fracture (<2 years) compared with observed calibration ratio. MOF, major osteoporotic fracture. Boldface font indicates evidence of higher risk from recent fracture with a p-value < $\alpha = 0.05$.

Table 4 Calibration ratios for incident hip fracture (observed vs predicted 10-year fracture probability with 95% confidence interval) and mean recent-fracture multiplier, analyzed according to age and prior fracture recency (N=33,465 women age 40-64 years, N=33,806 age ≥ 65 years).

Age 40-64 years	No prior fracture	≥ 2 years	< 2 years	Mean multiplier
Any Prior MOF	1.10 (0.92-1.27)	1.00 (0.63-1.36)	1.21 (0.75-1.67)	1.61
Prior Vertebral	1.09 (0.94-1.24)	1.06 (0.28-1.85)	1.45 (0.29-2.61)	1.80
Prior Hip	1.09 (0.94-1.24)	0.79 (0.00-1.88)	1.19 (0.16-2.22)	3.62***
Prior Humerus	1.06 (0.91-1.20)	1.91 (0.72-3.09)	2.12 (0.50-3.73)	0.95
Prior Forearm	1.07 (0.91-1.23)	1.38 (0.86-1.90)	0.95 (0.41-1.50)	1.51*
Age ≥ 65 years	No prior fracture	≥ 2 years	< 2 years	Mean Multiplier
Any Prior MOF	1.11 (1.04-1.18)	1.12 (0.98-1.25)	1.11 (0.93-1.29)	1.21
Prior Vertebral	1.30 (1.23-1.37)	1.31 (0.97-1.64)	0.97 (0.64-1.30)	1.24
Prior Hip	1.30 (1.23-1.37)	1.00 (0.70-1.29)	1.22 (0.86-1.57)	1.31
Prior Humerus	1.30 (1.22-1.37)	1.14 (0.87-1.42)	1.38 (0.94-1.82)	1.00
Prior Forearm	1.33 (1.26-1.41)	1.08 (0.92-1.24)	1.17 (0.86-1.47)	1.25

* p<0.05; ** p<0.01, *** p<0.001 for recent-fracture multiplier in those with recent fracture (<2 years) compared with observed calibration ratio. MOF, major osteoporotic fracture.